ACUTE TOXICITY SUMMARY

CHLOROFORM

(trichloromethane, formyl trichloride, methenyl trichloride, methyl trichloride)

CAS Registry Number: 67-66-3

I. Acute Toxicity Summary (for a 7-hour exposure)

Inhalation reference exposure level	**150 µg/m³**
Critical effect(s)	histological changes in the nasal epithelium
Hazard Index target(s)	Respiratory System; Nervous System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless liquid
Molecular formula	$CHCl_3$
Molecular weight	119.49
Density	1.483 g/cm^3 @ 20°C
Boiling point	61°C
Melting point	-63.5°C
Vapor pressure	200 mm Hg @ 25°C
Flashpoint	not applicable; non-flammable liquid, vapor will burn at high temperatures
Explosive limits	not applicable
Solubility	soluble in water, carbon tetrachloride, carbon disulfide, alcohols, benzene, ethers, oils
Odor threshold	192 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, suffocating (AIHA, 1989)
Metabolites	carbon dioxide, phosgene
Conversion factor	1 ppm = 4.88 mg/m³ @ 25°C

III. Major Uses or Sources

Chloroform ($CHCl_3$) is used in industry and laboratory settings as a solvent for adhesives, pesticides, fats, oils, and rubbers. It is also used as a chemical intermediate for fluorocarbon 22, dyes, pesticides, and tribromomethane. It is produced as a byproduct of water and sewage chlorination. Chloroform is also produced in large quantities as a byproduct of wood pulp chlorination in the production of paper products.

IV. Acute Toxicity to Humans

In humans, pulmonary excretion was found to be the major means of elimination following a single oral dose of 0.5 or 1.0 g $CHCl_3$ (Fry *et al*., 1972). Up to 68% of the unchanged $CHCl_3$ and up to 50.6% of the metabolite carbon dioxide were found in the expired air within eight hours of administration. Chloroform in the urine accounted for less than 1% of the oral dose.

Signs of acute $CHCl_3$ toxicity include fainting, vomiting, dizziness, salivation, fatigue, headache, respiratory depression, and coma (IRIS, 1993). Few reports were found in the literature on the acute toxicity of $CHCl_3$ to humans in chamber studies. However, a number of case reports exist stemming from its use an anesthetic.

Cardiac arrhythmia, brachycardia, and cardiac arrest resulting in death have been reported following the use of $CHCl_3$ as an anesthetic in concentrations of approximately 8,000 to 22,500 ppm (39,000 to 110,000 mg/m³) (Payne, 1981). Severe liver and kidney damage were noted in an adult male following fatal suicidal ingestion of approximately 6 ounces of $CHCl_3$ (Piersol *et al*., 1933).

The incidence of liver enlargement and jaundice was increased in workers exposed to 2-204 ppm (10-995 mg/m³) $CHCl_3$ for at least one year (Bomski *et al*., 1967). Jaundice was reported in 31 workers occupationally exposed to 14-400 ppm (68-1,952 mg/m³) $CHCl_3$ for 6 months or less (Phoon *et al*., 1983).

Predisposing Conditions for Chloroform Toxicity

Medical: Persons with skin, eye, respiratory, liver, kidney or neurological conditions may be more sensitive to the effects of chloroform (Reprotext, 1999).

Chemical: Epinephrine (e.g., in bronchodilators) may potentiate the cardiac effects of chloroform exposure (Reprotext, 1999). Concurrent exposure to barbiturates has been shown to increase chloroform toxicity by induction of liver cytochrome P-450 activity (Cornish *et al*., 1973). The potentiation of chloroform-induced hepatotoxicity and nephrotoxicity by various alcohols and ketones is well documented (Cowlen *et al*., 1984; Iijima *et al*., 1983; Brown and Hewitt, 1984.)

V. Acute Toxicity to Laboratory Animals

Beagle dogs exposed to 14,500 ppm (70,800 mg/m³) $CHCl_3$ survived an average of 202 minutes (Von Oettingen *et al*., 1949). The oral LD_{50} in male and female adult Sprague-Dawley rats is reported as 908 mg $CHCl_3$/kg and 1,117 mg $CHCl_3$/kg, respectively (Chu *et al*., 1980).

Hepatocellular necrosis was observed in adult female mice following a single 4-hour exposure to 200 ppm (976 mg/m³) $CHCl_3$ (Kylin *et al*., 1963). Hepatic fatty infiltration was noted following a single 4-hour exposure to 100 ppm (488 mg/m³) $CHCl_3$. Some studies report that chloroform

renal toxicity is gender-dependent, while hepatotoxicity is similar in both sexes (Smith *et al*., 1983 and 1984; Hill *et al*., 1975; Pohl *et al*., 1984; Taylor *et al*., 1974).

Cytochrome P-450-mediated metabolism of $CHCl_3$ in the liver and kidneys has been demonstrated to produce phosgene in rats (Pohl *et al*., 1979). Hepatotoxicity following chloroform exposure is thought to be due largely to phosgene and other reactive $CHCl_3$ metabolites. Metabolism of $CHCl_3$ to phosgene is also responsible for the nephrotoxicity of $CHCl_3$ (Bailie *et al*., 1984).

Male rats were exposed to 1, 3, 10, 30, 100, or 300 ppm $CHCl_3$ 6 hours per day for 7 days (Mery *et al*., 1994). Statistically significant, concentration-dependent, bony proliferation was observed in the ethmoid turbinates of rats exposed to 10 ppm $CHCl_3$ or greater. Cellular hypertrophy and proliferation in the nasal pharyngeal and olfactory mucosal regions were also increased in a concentration dependent manner in rats exposed to 10 ppm $CHCl_3$ or greater. No adverse effects were observed following exposure to 3 ppm (15 mg/m^3) $CHCl_3$.

VI. Reproductive or Developmental Toxicity

Pregnant rats were exposed to 30, 100, or 300 ppm (150, 500, or 1,500 mg/m^3) $CHCl_3$ for 7 hours per day on days 6-15 of gestation (Schwetz *et al*., 1974). A significant increase in the number of fetal resorptions and a decrease in fetal body weights and crown-rump lengths were observed in those animals exposed to 300 ppm $CHCl_3$. Following maternal exposure to 100 ppm $CHCl_3$, fetuses exhibited a significant increase in malformations including acaudia, imperforate anus, missing ribs and delayed sternal ossification. An increase in the incidence of wavy ribs and delayed skull ossification, as well as reduced fetal crown-rump length, were observed following maternal exposure to 30 ppm $CHCl_3$. Maternal toxicity was observed in all three exposure groups.

The incidence of abnormal sperm was significantly increased in male mice exposed to 400 ppm (1,952 mg/m^3) $CHCl_3$ for 4 hours/day for 5 days (Land *et al*., 1981).

Chloroform has not been listed as a developmental or reproductive toxicant under Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels

Reference Exposure Level (level protective against severe adverse effects; estimated for 7 hour exposure): 0.03 ppm (150 μg/m^3)

Study	Schwetz et al (1974)
Study population	pregnant rats
Exposure method	inhalation exposures to 30, 100, 300 ppm for 7 h/d, days 6-15 of gestation
Critical Effect	fetotoxicity
LOAEL	30 ppm
NOAEL	not determined
Exposure duration	7 hours/day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Reference Exposure Level (7 *h*)	0.03 ppm (0.15 mg/m^3; 150 μg/m^3)

The study by Schwetz *et al*. (1974) is the only published developmental toxicity study of chloroform. Exposure of pregnant rats to 30 ppm (150 mg/m³) $CHCl_3$ for 7 hours per day on days 6-15 of gestation resulted in fetotoxicity as indicated by decreased crown-rump length and increased incidences of wavy ribs and skeletal ossification defects. Maternal toxicity was also observed. An abstract by Dilley *et al*. (1977) indicates an absence of teratological effects in rats exposed to 20,000 mg/m³ $CHCl_3$ on days 7-14 of gestation. The data from this study were not available for review, therefore, the Schwetz *et al*. study is used in developing the severe adverse effect level for chloroform. A NOAEL was estimated from the reported LOAEL using an uncertainty factor of 10. An additional uncertainty factor of 100 was applied to account for inter- and intraspecies differences. The level protective against severe adverse effects for a 7 hour exposure is estimated as 0.03 ppm (0.15 mg/m³).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database. NIOSH (1995) lists a (revised) IDLH of 500 ppm based on acute inhalation toxicity in humans but the selection of the level is somewhat arbitrary and the IDLH does not make allowance for sensitive individuals.

VIII. References

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